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10/509,921	06/22/2005	Adam T. Gates	P51335	3826

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EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	**PAPER NUMBER**
1648	

NOTIFICATION DATE	DELIVERY MODE
09/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/509,921	GATES ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 14-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/16/2007 and 10/1/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received August 13, 2007.

Election/Restrictions

Applicant's election with traverse of group I, claims 1-8, 16, 17, and 18 and SEQ ID NO: 7 is acknowledged. Claims 14 and 15 amended to depend from elected claim 6 are rejoined. Applicant's request for rejoinder of process claims 17, 20, and 21 is acknowledged. Claims 17, 20 and 21 are rejoined. Claims 1-8, and 14-21 are under examination in the present Office action.

Applicants argue that Hong et al. (US 2001/0034019) cited in the restriction requirement of 5/11/2007, does not disclose the special technical feature of the present invention. Applicants argue that the GBV-B genomes disclosed by Hong et al. are not sub-genomic viral replicons, as the term is understood in the art and defined in the instant specification. Applicants direct to the definition of the sub-genomic replicon in the instant specification defining the sub-genomic replicons as a viral nucleic acid that contains something less than full complement of genes and other features of the viral genome, yet it is capable of directing the generation of copies of itself. The Office agrees that Hong's GBV-B genomes are not the sub-genomic replicons as they are defined in the instant specification. However the Office cites another reference by Selby et al. (US Patent 6,660,471 B2) that does disclose the sub-genomic replicons of the present invention. Selby et al. define their sub-genomic replicons as a viral nucleic acid that contains something less than the full complement of genes and other features of the viral genome, yet is still capable of directing the generation of copies of itself (see column 3, lines 15-34). It is noted that the definition of Selby's sub-genomic replicon and the definition of the sub-genomic replicon of the

instant invention are exactly the same. Thus, because Selby et al. disclose the sub-genomic replicons as they are defined in the present specification, Selby et al. disclose the special technical feature of the present invention.

Applicants elected SEQ ID NO: 7 without traverse for the purpose of initial examination to the extent that the election requirement was a species election. Applicants traverse the restriction requirement between individual sequences in the event that the election requirement was a restriction requirement. Applicants argue that SEQ ID NO: 2, 7, and 8 share 84% identity across their entire length as shown in provided sequence alignment. Applicants further argue that SEQ ID NO: 2, 7, and 8 share common structural properties and common utility, and therefore may not be restricted for the purpose of examination. Applicants arguments are found persuasive and the restriction requirement between SEQ ID NO: 2, 7, and 8 is withdrawn. The species of SEQ ID NO: 7 will be initially examined, and in the event that one or more generic claims are found allowable, additional species will be examined.

With regard to Applicants argument about that Examiner did not show how searching all inventions would be burdensome or that inventions have separate classification, the Office notes that the present Application was filed under 35 U.S.C. 371 and the U.S. national stage applications which entered the national stage from international applications after compliance with 35 U.S.C. 371 are subject to unity of invention practice in accordance with 37 CFR 1.475 and 1.499 (effective May 1, 1993) (see MPEP 1896). Therefore for Applications filed under 35 U.S.C. 371, the search burden or invention classification will not be established. The restriction requirement is deemed proper and is made FINAL.

Priority

Acknowledgment is made for priority to PCT/US03/10177, which claims benefit of 60/369,685.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/16/2007 and 10/1/2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Objection

Claim 2 is objected to for reciting "(portion language page 10, beginning in the first full paragraph)". Applicant is required to delete text that does not belong to the claim language.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, and 14-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims are drawn to a chimeric sub-genomic viral replicon capable of stably replicating in a human liver cell comprising: a replicon backbone from HCV strain BB7, a nucleic acid encoding at least one HCV nonstructural proteins from a strain other than BB7, a nucleic acid encoding an NS5B polymerase, and an HCV 3' NTR, wherein at least a portion of

the NS5B polymerase and the HCV 3'NTR are from the same HCV strain. The chimeric replicon comprises a portion of a nonstructural protein from a strain of HCV and a portion of a nonstructural protein from a different strain of HCV.

The claims are rejected because the present specification does not provide an adequate written description for **1)** the claimed genus of portions of the structural HCV NS5B polymerase of strain BB7 and **2)** portions of other nonstructural proteins of other HCV strains.

The present claims pertain to a function of the claimed chimeric sub-genomic replicons: capable of stably replicating in human liver cells, while the structures of the claimed replicons are not adequately described in the specification. Claiming a product based on its function does not provide written description for the product as claimed. The skilled artisan would be unable to decipher the structures of the claimed portions of the nonstructural HCV proteins. Thus the artisan would be unable to construct the chimeric HCV replicons of the present invention wherein the replicons posses the required function to stably replicate in human liver cells. The art teaches that while some mutations within the NS5A protein of HCV enhance the replication of the sub-genomic replicons, other mutations ablate the replicon translation and consequently formation of stable colonies in Huh-7 cells (see Gu et al. Journal of Virology, 2003, Vol. 77, p. 5352-5359). Thus in view of the art teachings, the skilled artisan would recognize that the portions of the nonstructural proteins comprised within the claimed replicons may or may not contribute to stable replication of the replicons.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or

chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of a portion of a nonstructural protein. There is lack of identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of genus of portions of the tructural HCV NS5B polymerase of strain BB7 or portions of other nonstructural proteins of other HCV strains, and therefore conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Thus in view of the discussion above it is determined that Applicant was not in possession of the claimed invention at the time when the Application was filed.

Claims 1-8, and 14-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chimeric sub-genomic viral replicons comprising

replicon backbone from strain BB7 and a nucleic acid from HCV strains H77, and J4 (as discloses in current Examples 1-4) capable of stably replicating in a Huh-7 human hepatoma cell line *in vitro*, does not reasonably provide enablement for chimeric sub-genomic viral replicon comprising nonstructural proteins from any other strains, and replicating in any other human liver cells other than Huh-7 human hepatoma cell line. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims are drawn to a chimeric sub-genomic viral replicon capable of stably replicating in a human liver cell comprising: a replicon backbone from HCV strain BB7, a nucleic acid encoding at least one HCV nonstructural proteins from a strain other than BB7, a nucleic acid encoding an NS5B polymerase, and an HCV 3' NTR, wherein at least a portion of the NS5B polymerase and the HCV 3'NTR are from the same HCV strain. The chimeric replicon comprises a portion of a nonstructural protein from a strain of HCV and a portion of a nonstructural protein from a different strain of HCV.

The claims are rejected because the present specification does not provide an adequate enablement for **1)** the broadly claimed human liver cells, **2)** broadly claimed nonstructural proteins from a strain other than BB7, and **3)** the claimed portions of the nonstructural HCV NS5B polymerase of strain BB7 or portions of other nonstructural proteins of other HCV strains.

Claims 4-8, and 14-16 drawn to specific structural embodiments of the claimed replicon are presently rejected because although some of the structural limitations recited in claims 4-8, and 14-16 are enabled when practiced in Huh-7 cells, those structural limitations are not enabled as being practiced in any human liver cells as recited in independent claim 1.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors deemed relevant are those of the amount of direction and the working examples provided, that quantity of experimentation necessary, the (un) predictability of the art, and the breadth of the claims.

The claims are broadly drawn to a chimeric sub-genomic viral replicon capable of stably replicating in a human liver cell. Thus the claims broadly encompass primary human liver cells (that are not transformed cell lines) and human liver cells of the liver *in vivo* in a human. The present specification does not provide an adequate enablement for replicating the chimeric sub-genomic viral replicons of the present invention in human liver cells *in vivo* or in primary human liver cells *in vitro*. The state of the prior and current art provides knowledge that the only human hepatoma cell lines that are capable of supporting replication the HCV sub-genomic viral replicons are Huh-7 human hepatoma cell line (see Lohman, et al, 1999, Science, Vol. 285, p. 110-113, in IDS of 10/1/2004, US Patent 6,660,471 B2, Gates et al, Virus Research, 2004, Vol. 100, p. 213-222, and Gu et al. Journal of Virology, 2003, Vol. 77, p. 5352-5359). The Examples of the present specification (particularly Example 2) show that Huh-7 cell lines are capable of

supporting replication the HCV sub-genomic viral replicons. The Examples do not provide sufficient support in order to allow one skilled in the art to conclude that human hepatoma cells other than Huh-7 cells can support replication of the chimeric replicons of the present invention. Therefore the instant specification does not enable the person skilled in the art to practice the invention commensurate with the scope of the present claims.

The claims broadly encompass chimeric sub-genomic replicons comprising a replicon backbone from HCV strain BB7 and a nucleic acid encoding portions of structural proteins from all known strains besides BB7 strain. The art teaches numerous HCV strains, in addition to BB7 strain (see Doi et al, Journal of Clinical Microbiology, 1996, Vol. 34, p. 569-574, Figure 3). The art also teaches while some subgenomic HCV replicon constructs posses the capability to stably replicate in Huh-7 cell lines, many other HCV replicon constructs fail to replicate and generate stable colonies in Huh-7 cells due inefficient translation of the replicon in Huh-7 cells (see Gu et al. Journal of Virology, 2003, Vol. 77, p. 5352-5359) and because of the absence of an interaction between the NS proteins and the 3'NTR (Gates et al, Virus Research, 2004, Vol. 100, p. 213-222). Gates et al. constructed a panel of chimera replicons containing non-structural NS and 3'NTR sequences from different HCV strains or types and examined the requirements for stable replication. Gates et al. have shown that a sub-genomic replicon chimera comprising the polymerase and 3'NTR from HCV strain Con1, and other nonstructural genes from type 1a strain H77 supported stable colony formation and replication in Huh-7 cells. However the similar chimera containing HCV strain J4 sequences linked to Con1 NS5B resulted in defective HCV replication. Thus the knowledge in the art suggests that only particular chimeric sub-genomic HCV replicons will have the capability to stably replicate in the Huh-7 cell lines while other

HCV replicons will fail to replicate. The skilled artisan would require to conduct an undue amount of experimentation in order to experimentally test which portions of which other HCV strains will successfully replicate when assembled into a HCV chimeric replicon.

The present specification provides evidence that particular specific HCV chimeric sub-genomic replicons have the ability to replicate in Huh-7 cells in vitro (see Examples 1-4). The specification does not provide an adequate enablement for sub-genomic chimeric HCV replicons comprising portions of nonstructural proteins from strains other than BB7 strain. Therefore the specification does not enable the skilled artisan to practice the invention commensurate with the scope of the present claims.

Thus, in view of the breadth of the claims, the limited guidance in the specification, and the unpredictability in the art, it is determined the skilled artisan would be unable to practice the full scope of the claimed invention.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 6,660,471 B2 discloses sub-genomic replicons, but it does not disclose or suggest chimeric sub-genomic replicons comprising HCV strain BB7 combined with nonstructural proteins from a strain other than BB7.

Conclusion

SEQ ID NO: 7 is free of prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035.

The examiner can normally be reached on Monday through Friday between 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AB

Agnieszka Boesen, Ph.D.

/Stacy B. Chen/ 9-17-07
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